REMARKS

Interview request

Applicants respectfully request a telephonic interview after the Examiner has reviewed the instant response and amendment. Applicants request the Examiner call Applicants' representative at (858) 720-5133.

Status of the Claims

Pending claims

Claims 1 to 4, 6 to 12, 14 to 17, 47, 48, 74 to 80, 84 to 86, 88, 89, 92, 93, 102 to 108, 112 to 116 and 118 to 124 are pending. Claims 74, 108, 112 to 116 and 118 to 121 remain withdrawn. Thus, claims 1 to 4, 6 to 12, 14 to 17, 47, 48, 75 to 80, 84 to 86, 88, 89, 92, 93, 102 to 107 and 122 to 124 are pending and currently under consideration.

Claims added and canceled in the instant amendment

In the present response, claims 125 to 135 are added. Thus, after entry of the instant amendment, claims 1 to 4, 6 to 12, 14 to 17, 47, 48, 75 to 80, 84 to 86, 88, 89, 92, 93, 102 to 107 and 122 to 135 will be pending and under consideration.

Claims allowed and objected to

Applicants thank the Examiner for finding claim 3 allowable, and only objecting to claims 14 and 15, noting they would be allowable if rewritten in independent form.

Restriction Requirement

In the Restriction Requirement mailed May 22, 2003, the Patent Office alleged that the pending claims of the application were directed to eight hundred and ninety-nine (899) separate and distinct inventions under 35 U.S.C. §121. In response, Applicants elected Group 62, for the nucleic acid having a sequence as set forth in SEQ ID NO:125, vectors, host cells, probes and a method of making the encoded polypeptide (SEQ ID NO:126), with traverse and argument.

Rejoining process claims

As noted in their response of February 24, 2004, Applicants respectfully requested that, after the elected product claims have been found to be allowable, all withdrawn process (methods) claims which depend from or otherwise include all of the limitations of the allowed product claims be rejoined. MPEP §821.04; pg 800-63, 8th Edition, August 2001; In re Ochiai, 37 USPQ2d 1127 (Fed. Cir. 1995); In re Brouwer, 37 USPQ2d 1663 (Fed. Cir. 1995); 1184 OG 86, 3/26/96.

Outstanding Rejections

Claims 7 to 9 are rejected under 35 U.S.C. §112, second paragraph. The rejection of claims 10 to 12, 17, 48, 75 to 80, 84 to 86, 88, 89, 92, 93 and 102 to 107 under 35 U.S.C. §112, first paragraph, is maintained for allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention (written description requirement). The rejection of claims 1 to 18, 47, 48, 74 to 89, 92, 93 and 102 to 108, 112 to 116 and 118 to 120 are rejected under 35 U.S.C. §112, first paragraph, is maintained because the specification allegedly does not reasonably provide enablement for the claimed invention (enablement requirement). The rejection of claims 2, 4, 7 to 12, 17, 47, 48, 75 to 80, 84 to 86, 92, 102 to 107, is maintained and claims 123 and 124 are newly rejected under 35 U.S.C. §102(b) under 35 U.S.C. §102(b) as allegedly anticipated by Tachibana et al. (Database GenBank, US National Library of Medicine (Bethesda, MD, USA), No. D83793, TACHIBANA et al., 01 February 2000) ("Tachibana").

Applicants respectfully traverse all outstanding objections to the specification and rejection of the claims.

Support for Claim Amendments

Support for the new and amended claims can be found throughout the application for the skilled artisan. For example, support for claims directed to nucleic acids and polypeptides of the invention of various lengths and identities can be found, inter alia, in paragraph 74, page 17; paragraphs 201 to 203, pages 50 to 51; paragraphs 237-239, pages 60-61; paragraphs 251-252,

pages 64-66, of the specification. Applicants submit that no new matter is introduced by the present amendments. Support for claims directed to probes comprising a nucleic acid comprising at least 500 consecutive bases of a sequence of the invention, wherein the probe can identify or isolate an amylase-encoding gene by hybridizing to the gene under specified conditions, can be found, inter alia, in paragraphs 0182 to 0202, on pages 45 to 51.

Claim Objections

Claims 6 and 124 are objected to under 37 CFR 1.75(c); see page 3, lines 4 to 19, of the instant office action ("the OA"). The instant amendment addresses these issues.

Issues under 35 U.S.C. §112, second paragraph

Claims 7 to 9 stand rejected under 35 U.S.C. §112, second paragraph, for allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. The Patent Office is concerned about the clarity of to which sequence the identity must be found (see page 4, lines 3 to 9, of the OA). The instant amendment addresses this issue.

Issues under 35 U.S.C. §112, first paragraph

Written Description

The rejection of claims 10 to 12, 17, 48, 75 to 80, 84 to 86, 88, 89, 92, 93 and 102 to 107 under 35 U.S.C. §112, first paragraph, is maintained for allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention.

Applicants respectfully submit that the claimed invention is sufficiently described in the specification so that one of ordinary skill in the art would be able to ascertain the scope of the claims with reasonable clarity and recognize that Applicants' were in possession of the claimed invention at the time of filing. Applicants respectfully submit that describing a genus of polynucleotides in terms of physico-chemical properties (e.g., a % sequence identity or stringent hybridization to an exemplary nucleic acid or polypeptide, e.g., SEQ ID NO:125 or SEQ ID

NO:126) and function (e.g., encoding a polypeptide having alpha amylase activity) satisfies the written description requirement of section 112, first paragraph.

Applicants respectfully aver that the disclosed alpha amylase-encoding nucleic acid species of the claimed invention, including SEQ ID NO:125, are sufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genera. As discussed in Applicants' previous responses (all expressly incorporated herein), both the Patent Office and the Federal Circuit have set forth conditions where a single species is sufficient to put one of skill in the art in possession of the attributes and features of all species within a genus, where the genus is defined in terms of shared physical and structural properties with the single species.

The Federal Circuit has addressed the written description requirement in the context of biological sequences in Enzo Biochem. Inc. v. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that "the written description requirement can be met by 'showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics . . . *i.e.*, complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.'" [Emphasis added] Id. at 1324, 63 USPQ2d at 1613. The court in Enzo adopted its standard from the USPTO's Written Description Examination Guidelines. See 296 F.3d at 1324, 63 USPQ2d at 1613 (citing the Guidelines). The Guidelines apply to proteins as well as DNAs. The Enzo court also stated:

> Similarly, in this court's most recent pronouncement, it noted:
>
> More recently, in Enzo Biochem, we clarified that Eli Lilly did not hold that all functional descriptions of genetic material necessarily fail as a matter of law to meet the written description requirement; rather, the requirement may be satisfied if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure.

Amgen, 314 F.3d at 1332 [Amgen Inc. v. Hoechst Marion Roussel Inc., 314 F.3d 1313, 1330, 65 USPQ2d 1385, 1397 (Fed. Cir. 2003)]. Moba, B.V. v. Diamond Automation, Inc., 2003 U.S. App. LEXIS 6285; Fed. Cir. 01-1063, -1083, April 1, 2003.

Analogously, the structure of all of the species within the claimed genus of nucleic acids encoding alpha amylases are sufficiently correlated to a particular, known structure (the exemplary SEQ ID NO:125 or SEQ ID NO:126); a physical property (percent sequence identity or stringent hybridization), and function (alpha amylase activity). Accordingly, this genus of nucleic acids is defined via shared structural and functional properties in terms that convey with reasonable clarity to those skilled in the art that Applicants, as of the filing date and at the time of the invention, were in possession of the claimed invention.

The claimed subject matter need not be described in haec verba to satisfy the description requirement. It is not necessary that the application describe the claim limitations exactly, but only so clearly that one having ordinary skill in the pertinent art would recognize from the disclosure that applicants invented the claimed subject matter. In re Herschler, 591 F.2d 693, 700, 200 USPQ 711,717 (CCPA 1979). See also Purdue Pharma L.P. v. Faulding, Inc., 230 F.3d 1320, 1323, 56 USPQ2d 1481, 1483 (Fed. Cir. 2000) ("In order to satisfy the written description requirement, the disclosure as originally filed does not have to provide in haec verba support for the claimed subject matter at issue.").

Applicants also have noted that the USPTO guidelines concerning compliance with the written description requirement of U.S.C. §112, first paragraph, particularly Example 14, state that a description of a genus of polynucleotides in terms of its physico-chemical properties, e.g., a % sequence identity, to a single exemplary species, and a common function satisfies the written description requirement of section 112, first paragraph, for the genus of polynucleotides.

Example 14 used a claim reciting variants claimed by sequence identity to an exemplary sequence ("A protein having SEQ ID NO:3 and variants thereof that are at least 95% identical to SEQ ID NO:3 and catalyze the reaction of A → B). The specification of the example contemplated, but did not exemplify variants of SEQ ID NO:3 that can have substitutions, deletions, insertions and additions. Procedures for making proteins with substitutions, deletions, insertions, and additions were noted to be routine in the art and an assay was described which could identify other proteins having the same claimed catalytic activity. Procedures for making these variants (which have 95%

sequence identity) were conventional in the art. The Guideline's conclusion stated that the disclosure met the requirements of 35 U.S.C. §112, first paragraph, as providing adequate written description for the claimed invention.

Analogously, the nucleic acid and amino acid sequences of the claimed genus are described by structure (the exemplary nucleic acid (SEQ ID NO:125) and polypeptide (SEQ ID NO:126)), a physico-chemical property (percent sequence identity or stringent hybridization) and function (alpha amylase activity). The claimed genus of polypeptides all must have, or encode a polypeptide having, alpha amylase activity and a specific sequence identity (e.g., 85%, 90%, 95%, 97%, 98% or 99%) to SEQ ID NO:125 or 126, or, hybridize under stringent conditions to SEQ ID NO:125. Because the Guidelines recognized that the written description requirements are met for a genus of polypeptides described by structure, a physico-chemical property (e.g., a % sequence identity, stringent hybridization) and a defined function, the genus of claimed polypeptides also meet the written description requirements of section 112.

The Office remains concerned that, allegedly, "no description has been provided of the structure and function of the modified polynucleotide sequences encompassed by the claims (see, e.g., page 5, lines 13 to 22, of the OA)" and that the specification does not contain any disclosure of the structure and function of all the polynucleotide sequences derived from SEQ ID NO:125. However, Applicants respectfully aver that the specification describes the claim limitations sufficiently clearly that one having ordinary skill in the pertinent art would recognize from the disclosure that Applicants invented the claimed subject matter. The nucleic acid and amino acid sequences of the claimed genus are described by structure (the exemplary nucleic acid SEQ ID NO:125 and polypeptide SEQ ID NO:126), a physico-chemical property (percent sequence identity or stringent hybridization) and function (alpha amylase activity). As emphasized by Example 14 of the USPTO guidelines, it is not necessary for the specification to specifically exemplify sequence variants to satisfy the written description requirement. Thus, the claimed genus of nucleic acids encoding alpha amylases are defined via shared physical and structural properties set forth in the specification in terms that convey with reasonable clarity to those skilled in the art that Applicants, as of the filing date and at the time of the invention, were in possession of the claimed invention.

The Office also remains concerned that structurally unrelated polynucleotides are encompassed within the scope of the claims (see, e.g., page 6, lines 8 to 10, of the OA). However, only structurally and functionally related nucleic acid and amino acid sequences fall within the scope of the claimed genus – these sequences are described by structure (the exemplary nucleic acid SEQ ID NO:125 and polypeptide SEQ ID NO:126 – and fragments thereof), a physico-chemical property (percent sequence identity or stringent hybridization) and function (alpha amylase activity).

The Office considered Applicants' last argument incorporating, inter alia, Example 14 of the USPTO written description guidelines, but alleged that claims 17, 75 to 80, 84 to 86, 88, 89, 92 or 93, have no functional limitations (see, e.g., page 7, lines 8 to 14, of the OA). The instant amendment addresses this issue. The instant amendment clarifies that all probe sequences within the scope of the claimed invention have a functional limitation; for example, claim 17 (as currently amended) is directed to probes comprising a nucleic acid comprising at least 500 consecutive bases of a sequence of the invention, wherein the probe can identify or isolate an amylase-encoding gene by hybridizing to the gene under specific hybridization conditions. Claim 75 (as currently amended) is directed to nucleic acid probes for identifying or isolating an amylase-encoding gene, wherein the probe comprises an oligonucleotide at least about 50 nucleotides in length and having a segment of at least 50 contiguous nucleotides of a nucleic acid of the invention, and which hybridizes under specific hybridization conditions.

The Office also remains concerned that fragments consisting of only 50 to 200 residues having 90% to 97% identity to a portion of SEQ ID NO:125 are highly unlikely to have alpha amylase activity, and would constitute only a small portion of the structure of the exemplary species SEQ ID NO:125 (see, e.g., page 8, lines 16 to 22, of the OA). The instant amendment addresses these concerns. For example, claim 8, as currently amended, is drawn to nucleic acids encoding polypeptides having alpha amylase activity and having an amino acid sequence at least 99% sequence identity to SEQ ID NO:126 over a region of at least about 75 or 100 consecutive residues. Claim 9 as currently amended is drawn to nucleic acids encoding polypeptides having alpha

amylase activity and having an amino acid sequence at least 97% sequence identity to SEQ ID NO:126 over a region of at least about 150 consecutive residues.

The Office also remains concerned that recited structural features of the genus may not constitute a substantial portion of the genus because the remainder of the structure of a nucleic acid encoding a polypeptide with alpha amylase activity is completely undefined (see, e.g., page 8, lines 16 to 22, of the OA). It appears that the Office is concerned that "the remainder of the structure of a nucleic acid", or the unrecited structure of a nucleic acid in a claim directed to nucleic acids "comprising" other sequences, is not described. However, Applicants wish to clarify that they use the terms "comprises" or "comprising" as open-ended terms. The transitional terms "comprising" and "comprises" (and other comparable terms, e.g., "containing," and "including") are "open-ended" - they cover the expressly recited subject matter, alone or in combination with unrecited subject matter. See, e.g., Genentech, Inc. v. Chiron Corp., 112 F.3d 495, 501, 42 USPQ2d 1608, 1613 (Fed. Cir. 1997) ("`Comprising' is a term of art used in claim language which means that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim."); Ex parte Davis, 80 USPQ 448, 450 (Bd. App. 1948) ("comprising" leaves the "claim open for the inclusion of unspecified ingredients even in major amounts"). See also MPEP § 2111.03. MPEP §2163, section II.A.1., page 2100-169, Rev. 2, May 2004. Applicants need not enable or describe "unrecited subject matter" as encompassed by the term "comprising". It is inappropriate for the Office to require Applicants to enable or describe "unrecited subject matter" as encompassed by the term of art "comprising" to satisfy the requirement of section 112.

In light of the instant amendment and these remarks, Applicants respectfully submit that the claimed invention is sufficiently described in the specification so that one of ordinary skill in the art would be able to ascertain the scope of the claims with reasonable clarity and recognize that Applicants' were in possession of the claimed invention at the time of filing. Applicants respectfully submit that because the amended claims encompassing the claimed alpha amylase-encoding nucleic acids meet the written description requirement, the rejection under 35 U.S.C. §112, first paragraph, can be withdrawn.

Enablement

The rejection of claims 1 to 18, 47, 48, 74 to 89, 92, 93 and 102 to 108, 112 to 116 and 118 to 120 are rejected under 35 U.S.C. §112, first paragraph, is maintained because the specification allegedly does not reasonably provide enablement for the claimed invention.

The Patent Office notes that the specification is enabling for polynucleotides encoding the exemplary polypeptide SEQ ID NO:126.

Applicants respectfully aver that the specification enabled the skilled artisan at the time of the invention to identify, and make and use, the claimed genus of amylase-encoding nucleic acids to practice the invention. Applicants have provided sufficient evidence and expert declaration to support this argument, as set forth in their previous responses of August 20, 2004, and February 24, 2004, which are expressly incorporated herein.

Applicants also respectfully maintain that the Patent Office has not met its initial burden to establish a reasonable basis to question the enablement provided for the claimed invention, as set forth in Applicants' last response of August 20, 2004, pages 28 to 32. In order to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. MPEP §2164.05, 8th edition, rev. 2, May 2004, pg 2100-190 to -191.

The Patent Office cited Bork, et al., Broun et al., Van de Loo et al., Witkowski et al. and Seffernick et al. to show the "unpredictability of assigning function based on structural homology and how small changes can lead to major changes in function;" in other words, these references were cited to support the Offices' allegation of the unpredictability in this art. However, as discussed in detail in Applicants' last response (see pages 29 to 31 of that response), none of these references, individually or in their totality, are sufficient to rebut the presumption of enablement – these references do not support the allegation that the art was so unpredictable as to negate the application's presumption of enablement.

For example, Bork (2000) Genome Res. 10:398-400, discusses limits on computational sequence analysis. In Bork, there is no discussion regarding the merits or difficulties of protocols that screen for enzyme activity, e.g., screen for enzyme activity in a library of polypeptides expressed by a plurality of nucleic acid variants. Bork only questions the accuracy of assigning protein function based on sequence identity. However, the amylase activity of polypeptides of the instant invention are not based on sequence identity homology to known proteins, but rather are based on empirical, experimental data demonstrating that polypeptides of the invention have amylase activity (see, e.g., Example 1, page 83, of the specification). Interestingly, Bork opines that most computational sequence analysis methodologies can predict function with an expected accuracy of about 70%.

Broun et al. (1998) Science 282:1315-1317, shows that a small number of amino acid reside changes in the catalytic site of a family of structurally related enzymes can result in a change in activity (in particular, Broun found that as few as four amino acid substitutions can convert an oleate 12-desaturase to a hydroxylase and as few as six result in conversion of a hydroxylase to a desaturase). However, it appears that Broun considered screening for enzyme activity in their enzyme variants a routine process. There is no discussion on whether changes in non-catalytic site amino acid residues have any effect on enzyme activity. In fact, Broun's data suggest that most changes in an enzyme's amino acid sequence (e.g., non-catalytic site amino acid residues) are not important in determining, or changing, its catalytic specificity.

Van de Loo et al. (1995) Proc. Natl. Acad. Sci. USA 92:6743-6747, prepared a cDNA library from a castor-oil plant, obtained partial nucleotide sequences for 468 anonymous clones, identified several cDNA clones encoding a polypeptide of 387 amino acids with a predicted MW of 44,407 and with approximately 67% sequence homology to an oleate desaturase, and expressed a full-length clone in a transgenic tobacco, which resulted in the accumulation of low levels of 12-hydroxyoleic acid in seeds, indicating that the expressed clone encodes an oleate hydroxylase. Van de Loo opined that these results suggested that fatty acyl desaturases and hydroxylases share similar reaction mechanisms. However, in Van de Loo, there is no discussion regarding the merits or difficulties of protocols that screen for enzyme activity, e.g., screen for enzyme activity in a library

of polypeptides expressed by a plurality of nucleic acid variants. In fact, it appears that Van de Loo considered screening for enzyme activity in their single expressed clone a routine process. Van de Loo also credited the high-throughput capabilities of automated DNA sequenators in the examination of their anonymous clones.

Witkowski et al. (1999) Biochemistry 38:11643-11650, also showed that a small number of amino acid reside changes in the catalytic site of a family of structurally related enzymes can result in a change in activity. Witkowski noted that beta-ketoacyl synthases involved in the biosynthesis of fatty acids and polyketides exhibit extensive sequence similarity and share a common reaction mechanism. Interestingly, Witkowski also noted that multiple sequence alignments identified catalytic sites and provided the first clues about the possible identities of residues that play critical roles in catalysis. In fact, as with Broun, Witkowski's data suggest that most changes in an enzyme's amino acid sequence (e.g., non-catalytic site amino acid residues) are not important in determining, or changing, its catalytic specificity. In Witkowski, there is no discussion regarding the merits or difficulties of protocols that screen for enzyme activity, e.g., screen for enzyme activity in a library of polypeptides expressed by a plurality of nucleic acid variants. It appears that Witkowski considered screening for enzyme activity a routine process.

Seffernick et al. (2001) J. of Bacteriol. 183:2405-2410, also shows that a small number of amino acid reside changes in the catalytic site of an enzyme can result in a change in activity. Seffernick compared a deaminase (melamine deaminase) with a hydrolase (atrazine chlorohydrolase, AtzA) and found that each enzyme consists of 475 amino acids and differs by only 9 amino acids. Seffernick opined that their data suggest that the 9 amino acid differences between melamine deaminase and AtzA represent a short evolutionary pathway connecting enzymes catalyzing physiologically relevant deamination and dehalogenation reactions. As with Broun and Witkowski, Seffernick's data suggest that most changes in an enzyme's amino acid sequence (e.g., non-catalytic site amino acid residues) are not important in determining, or changing, its catalytic specificity. In Seffernick, there is no discussion regarding the merits or difficulties of protocols that screen for enzyme activity, e.g., screen for enzyme activity in a library of polypeptides expressed by

a plurality of nucleic acid variants. It appears that Seffernick considered screening for enzyme activity a routine process.

Accordingly, none of these references, individually or in their totality, are sufficient to rebut the presumption of enablement – these references do not support the allegation that the art was so unpredictable as to negate the application's presumption of enablement.

In the instant response (see, e.g., page 15, lines 15 to 20, of the OA), reiterates its use of these references to support the allegation of the unpredictability in this art, or specifically, how the cited art teaches the unpredictability of assigning function based on structural homology and how small structural changes can lead to major changes in function. The Office does not comment on Applicants' assertion that Bork, Broun, Witkowski, Van de Loo and Seffernick's data suggest that most changes in an enzyme's amino acid sequence (e.g., non-catalytic site amino acid residues) are not important in determining, or changing, its catalytic specificity, and that the references cited by the Office actually support the idea that most changes in an enzyme's amino acid sequence will result in little or no effect on its specificity or activity, and that one of skill in the art could easily target a minimum number of residues to generate a limited number of enzyme variants to generate desired enzyme variants.

The Patent Office maintained its allegations that it would not have been routine in the art to screen for multiple substitutions or multiple modifications of the exemplary sequences to make the claimed genus of nucleic acids (see, e.g., page 12, lines 10 to 20). The Office also remains concerned whether the specification need establish regions of protein structure which may be modified while producing variants having alpha amylase activity, as discussed on page 13, lines 1 to 10, of the OA. The Office acknowledged that Dr. Short addressed these issues in his expert Rule 132 declarations submitted with Applicants' responses of August 20, 2004, and February 24, 2004. However, the Office dismissed Dr. Short's declarations (see, e.g., page 16, line 12, to page 17, line 12), alleging it just to be a conclusion (see page 16, lines 12 to 15). (A declaration or affidavit is, itself, evidence that must be considered. The weight to give a declaration or affidavit will depend upon the amount of factual evidence the declaration or affidavit contains to support the conclusion

of enablement. In re Buchner, 929 F2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991) ("expert's opinion on the ultimate legal conclusion must be supported by something more than just a conclusory statement"; cf. In re Alton, 76 F3d 1168, 1174, 37 USPQ2d 1578, 1583. MPEP 2164.05, pg 2100-190, 8th ed., rev. 2, May 2004.

Dr. Short's declarations provide more that just conclusory statements. Dr. Short declared that the state of the art at the time of the invention and the level of skill of the person of ordinary skill in the art, e.g., screening enzymes, and nucleic acids encoding enzymes, for various amylase activities, e.g., alpha amylase activity, was very high - citing specific disclosure in the specification supporting this (e.g., see page 2 of the declaration submitted Aug. 20, 2004). The specification did provide the skilled artisan a reasonable amount of guidance with respect to screening for amylases, i.e., screening variant nucleic acids to identify the claimed genus of amylase-encoding nucleic acids. For example, Example 1, pages 83 to 84, describes a protocol to identify and characterize thermostable amylases; Example 2, pages 84 to 86, and Example 4, page 87, describe protocols to identify and characterize thermostable amylases at alkaline pH; Example 5, pages 87 to 89, and Example 6, pages 90 to 93, Example 7, pages 94 to 103, describe exemplary amylase activity assays; and, Example 9, page 105, describes a protocol to determine the pH optimum for an amylase activity (the hydrolysis of starch). Accordingly, the specification provides guidance on alternative, routine protocols for determining alpha amylase activity that can be practiced without undue experimentation.

Dr. Short also declared that at the time of the invention, high through-put *in vivo* (e.g., whole cell) and *in vitro* nucleic acid expression and enzyme (amylase) screening protocols were well known in the art, and using these high through-put screening assays with amylase assays known in the art, including those routine amylase screening assays described in the specification (see discussion, above), one of skill in the art could have routinely expressed variant nucleic acids and routinely identified amylase-encoding nucleic acids, i.e., screened for and identified the claimed genus of amylase-encoding nucleic acids without undue experimentation. Accordingly, it would not have taken undue experimentation to make and use the claimed invention, including screening for and identifying the claimed genus of amylase-encoding nucleic acids.

Furthermore, the Office presented no scientific evidence specifically its dismissal of Dr. Short's declarations. The examiner must weigh all the evidence before him or her, including the specification and any new evidence supplied by applicant with the evidence and/or sound scientific reasoning previously presented in the rejection and decide whether the claimed invention is enabled. The examiner should never make the determination based on personal opinion. The determination should always be based on the weight of all the evidence. MPEP §2164.05, 8th edition, rev. 2, May 2004, pg 2100-190 to -191. A declaration or affidavit is, itself, evidence that must be considered. MPEP 2164.05, pg 2100-190, 8th ed., rev. 2, May 2004. Applicants respectfully submit that the Office cannot dismiss Dr. Short's expert declarations in support of the enabling disclosure without citing specific support in rebuttal.

The Patent Office maintained its concerns that, inter alia, the specification does not establish regions of protein structure which may be modified while producing variants having alpha amylase activity. It was alleged, inter alia, that in the absence of any information as to how structure correlates with function, one of skill in the art would have to go through the burden of undue experimentation to isolate or make the claimed nucleic acids. See, e.g., page 17, line 12, to page 18, of the OA. The Office also notes that claim 3 is allowable. Claim 3 is directed to, inter alia, nucleic acids encoding a polypeptide having alpha amylase activity that hybridize under stringent conditions to SEQ ID NO:125 or complementary sequences under specifically cited stringent hybridization conditions.

Applicants maintain that the specification does provide guidance as to what "conservative" amino acid substitutions can be made to make and identify the genus of amylase-encoding nucleic acids of the invention. The Office alleges this guidance is generic (see, e.g., page 18, lines 9 to 12, of the OA). However, the specification, inter alia, in paragraph 0075, on pages 17 to 18, gives very specific guidance on what a "substantially identical" or "conservative" amino acid substitution can be, e.g., substituting one amino acid for another of the same class, such as substitution of one hydrophobic amino acid, such as isoleucine, valine, leucine, or methionine, for another, or substitution of one polar amino acid for another, such as substitution of arginine for lysine, glutamic acid for aspartic acid or glutamine for asparagine.

Applicants maintain that because the three dimension structure of amylases had been described, the skilled artisan had direction as to which amino acid residues can be modified and how structure correlates with function. Applicants also maintain that at the time of the invention one of skill in the art would have been aware of the many studies of amylase activity and active sites (with specific citations noted in Applicants' last response). Accordingly, one skilled in the art at the time of the invention, using the teaching of the specification (and including the teaching of the specification), had many sources of direction to determine which amino acid residues could be substituted, deleted or inserted into a nucleic acid to obtain structural, and functional, homologues of an enzyme.

Applicants respectfully maintain that it would not have been necessary for one skilled in the art to understand which specific regions of amylase structure could be modified to generate the genus of nucleic acids or polypeptides of the invention, for reasons discussed above (e.g., as noted by Dr. Short, it would not have required any knowledge or guidance as to which are the specific structural elements, e.g., amino acid residues, that correlate with amylase activity to create variants of the exemplary nucleic acid and test them for the expression of polypeptides or peptides having amylase activity).

Accordingly, Applicants respectfully submit that the pending claims meet the written description and enablement requirements under 35 U.S.C. §112, first paragraph. In light of the above remarks, Applicants respectfully submit that amended claims are fully enabled by and described in the specification to overcome the rejection based upon 35 U.S.C. §112, first paragraph.

Issues under 35 U.S.C. §102(b)

The rejection of claims 2, 4, 7 to 12, 17, 47, 48, 75 to 80, 84 to 86, 92, 102 to 107, is maintained and claims 123 and 124 are newly rejected under 35 U.S.C. §102(b) under 35 U.S.C. §102(b) as allegedly anticipated by Tachibana et al. (Database GenBank, US National Library of Medicine (Bethesda, MD, USA), No. D83793, TACHIBANA et al., 01 February 2000) ("Tachibana").

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987); MPEP § 2131.

The Patent Office notes that Tachibana teaches the isolation and expression of a polynucleotide encoding an alpha amylase having 80% sequence identity to SEQ ID NO:125, and encodes a protein having 85% identity to SEQ ID NO:126. The instant amendment addresses this issue. For example, claim 1 (as currently amended) is directed to isolated or recombinant nucleic acids comprising nucleic acids encoding a polypeptide having alpha amylase activity, wherein nucleic acids have at least 85% sequence identity to a sequence as set forth in SEQ ID NO:125; or nucleic acids comprising a sequence encoding a polypeptide having alpha amylase activity, wherein the sequence has at least 90% sequence identity to a sequence as set forth in SEQ ID NO:126. Claim 7 (as currently amended) is directed to sequences having at least 95% sequence identity to SEQ ID NO:125 over a region of at least about 200 consecutive residues, or 90% sequence identity to SEQ ID NO:125 over a region of at least about 300, 400 or 500 consecutive residues. Claim 8 (as currently amended) is directed to sequences having at least 99% sequence identity to SEQ ID NO:125 over a region of at least about 75 or 100 consecutive residues. Claim 9 (as currently amended) is directed to sequences having at least 97% sequence identity to SEQ ID NO:125 over a region of at least about 150 consecutive residues.

The Office also had concerns regarding claims 2, 4 and 17, and whether the sequence of Tachibana could hybridize under the specified stringent conditions to SEQ ID NO:125. The instant amendment addresses this issue. Claim 2 (as currently amended) is directed to nucleic acids that hybridize under specified conditions to SEQ ID NO:125, wherein the nucleic acid comprises a sequence encoding a polypeptide having alpha amylase activity, wherein the sequence has at least 85% sequence identity to a sequence as set forth in SEQ ID NO:125; or, a sequence encoding a polypeptide having alpha amylase activity, wherein the sequence has at least 90% sequence identity to a sequence as set forth in SEQ ID NO:126.

The Office also notes that the protein encoded by the gene of Tachibana comprises a region of 100 amino acids having greater than 98% identity to the entire sequence of SEQ ID NO:126. The Office alleges that sequence taught by Tachibana comprises a region of 75 amino acids having greater than 90% identity to SEQ ID NO:126. The instant amendment addresses this issue. For example, claim 123 (as currently amended), is directed to nucleic acids encoding a polypeptide having an amino acid sequence at least 99% sequence identity over a region of at least about 100 or 150 consecutive residues to SEQ ID NO:126.

In light of the instant amendment, Tachibana does not teach all of the elements of the amended claims. Accordingly, because Tachibana is not a single reference teaching each and every element of the claimed invention, withdrawal of the rejection under section §102 is respectfully requested.

Issues under 35 U.S.C. §103(a)

The rejection of claims 88 and 89 under 35 U.S.C. §103(a) as allegedly obvious over Tachibana in view of the state of the art has been maintained.

As discussed above, the instant amendment removes Tachibana as a single reference teaching each and every element of the claimed invention. The state of the art at the time of the invention does not cure the defect in Tachibana to teach the claimed (amended) sequences. Accordingly, the rejection of claims 88 and 89 under 35 U.S.C. §103(a) as allegedly obvious over Tachibana in view of the state of the art can be withdrawn.

CONCLUSION

In view of the foregoing amendment and remarks, it is believed that the Examiner can properly withdraw the rejection of the pending claims under 35 U.S.C. §112, first and second paragraphs, 35 U.S.C. §102 and 35 U.S.C. §103. Applicants believe all claims pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

As noted above, Applicants have requested a telephone conference with the undersigned representative to expedite prosecution of this application. After the Examiner has reviewed the instant response and amendment, please telephone the undersigned at 858 720 7943 or Gregory Einhorn at (858) 720-5133.

Applicants believe that no additional fees are necessitated by the present response and amendment. However, in the event any such fees are due, the Commissioner is hereby authorized to charge any such fees to Deposit Account No. 03-1952 referencing docket number 564462006100. Please credit any overpayment to this account.

Dated: April 5, 2005

Respectfully submitted,

By _____

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